UNITED STATES DEPARTMENT OF COMMERCE
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/636,778	08/11/00	SHORT J	DIVER1280-4

HM12/0410

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EXAMINER	
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ART UNIT	PAPER NUMBER
1636	3

DATE MAILED: 04/10/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/636,778	SHORT ET AL.	
	Examiner	Art Unit	
	Lisa Gansheroff	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-122* is/are pending in the application.

4a) Of the above claim(s) *1-53 and 74-122* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *54-73* is/are rejected.

7)☒ Claim(s) *57,64-66,70 and 71* is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *11 August 2000* is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 2 .
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other: .

Application/Control Number: 09/636,778
Art Unit: 1636

DETAILED ACTION

Pending claims: 1-122.

Response to: IDS filed 21 March 2001.

Claims drawn to the elected invention: 54-73.

Election/Restrictions

Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 1-53, drawn to a method to identify bioactivities or biomolecules by screening a gene library by encapsulating a substrate and a library clone, and/or by providing a gene library generated from the nucleic acid of more than one organism and inserting a substrate into the clones, classified in class 435, subclass 6.

II. Claims 54-73, drawn to a method of screening for an agent that modulates activity of a target cell component using co-encapsulation of the agent and a recombinant cell, classified in class 435, subclass 4.

III. Claims 74-99, drawn to a method to enrich for DNA sequences using co-encapsulation and DNA hybridization, classified in class 435, subclass 6.

IV. Claims 100-114, drawn to a method of screening for an agent that modulates the interaction between two test proteins by co-encapsulating the test proteins linked to DNA binding and transcriptional activation moieties, classified in class 435, subclass 4.

V. Claims 115-122, drawn to a method of identifying bioactivities or biomolecules comprising growing a mycelia-producing cell type and screening, classified in class 435, subclass 4.

The inventions are distinct, each from the other because of the following reasons:

Inventions I - V are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). In the instant case the different inventions comprise steps that are not required for and/or not present in the other methods. For example, Group I requires co-encapsulating a library clone with a substrate for a bioactivity or biomolecule and/or generating a library from nucleic acid from more than one organism. Group II requires screening for modulation of an activity by co-encapsulating a cell and an agent. Group III requires encapsulation and DNA hybridization. Group IV requires encapsulating proteins. Group V requires a mycelia-producing cell type and fluorescence screening but does not require encapsulation, hybridization, test proteins linked to DNA binding and transcriptional activation moieties, or screening for agents that modulate an activity. The effects of the different methods are also different: Group I identifies a nucleic acid from library clone based on a particular bioactivity with a given substrate; Group II identifies an agent that modulates an activity; Group III identifies DNA based on hybridization; Group IV identifies agents that affect a protein-protein interaction; and Group V identifies bioactivities produced by a mycelia-producing cell type.

Because these inventions are distinct for the reasons given above and have acquired a separate status in the art because of their recognized divergent subject matter, and because searches for the different Groups would not be coextensive, restriction for examination purposes as indicated is proper.

During a telephone conversation with Lisa Haile on 27 March 2001, a provisional election was made with traverse to prosecute the invention of Group II, claims 54-73. Affirmation of this election must be made by applicant in replying to this Office action. Claims 1-53 and 74-122 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a petition under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Drawings

The drawings are objected to because of the following. Figures 12-17 are partially obscured by the hole-punches in the top margins of the pages. Figures 1, 4, and 14-16 are of a copy quality that renders details difficult to see. Correction is required.

Specification

Applicant is reminded of the proper language and format for an abstract of the disclosure.

The abstract should be in narrative form and generally limited to a single paragraph on a separate sheet within the range of 50 to 250 words. It is important that the abstract not exceed 250 words in length since the space provided for the abstract on the computer tape used by the printer is limited. The form and legal phraseology often used in patent claims, such as "means" and "said," should be avoided. The abstract should describe the disclosure sufficiently to assist readers in deciding whether there is a need for consulting the full patent text for details.

The language should be clear and concise and should not repeat information given in the title. It should avoid using phrases which can be implied, such as, "The disclosure concerns," "The disclosure defined by this invention," "The disclosure describes," etc.

The abstract of the disclosure is objected to because it includes the legal phraseology "said". Correction is required. See MPEP § 608.01(b).

The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. The title is not descriptive of the elected invention.

Priority

If applicant desires priority under 35 U.S.C. 120 based upon a previously filed copending application, specific reference to the earlier filed application must be made in the instant application. This should appear as the first sentence of the specification following the title, preferably as a separate paragraph. The status of nonprovisional parent application(s) (whether patented or abandoned) should also be included. If a parent application has become a patent, the expression "now Patent No._____" should follow the filing date of the parent

application. If a parent application has become abandoned, the expression "now abandoned" should follow the filing date of the parent application.

In the instant application, the status of 09/098206 should be updated. The status of 08/876276 should be clarified as the instant specification states that it is abandoned, but the PTO database (PALM) does not list is as in abandoned status.

Claim Objections

Claim 57 is objected to because of the following informalities: Is "epozide", in the fourth line of the claim, a typographical error for "epoxide"? (See also specification page 37.)

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 54-73 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 54 recites the limitation "the recombinant cell" in the fourth line of the claim. There is insufficient antecedent basis for this limitation in the claim.

Claim 54 recites "selectable marker" in the second line and "detectable marker" in the fifth line. It is not clear if these are meant to be the same or different, and since claim 67 recites

that the detectable marker can be a "dye" or a "chemiluminescent molecule" or a "radioactive material", it is not clear what is meant in claim 54 by the phrase "with the recombinant cell expressing the ...detectable marker".

Claims 61 and 62 recite "the method of claim 54, wherein the cell is" a eukaryotic or prokaryotic cell, and claims 72 and 73 recite "the method of claim 54, wherein the recombinant cell is" a eukaryotic or prokaryotic cell. Since the phrase "the recombinant cell" in claim 54 lacks antecedent basis, it is not clear whether there is meant to be a difference between a "cell" and a "recombinant cell", and thus it is not clear whether claims 61 and 61 are essentially duplicates of claims 72 and 73, respectively.

Claim 70 recites the limitation "the protein". There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 102

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

Claims 54, 55, 58, 59, 62, 63, 67, 69, and 73 are rejected under 35 U.S.C. 102(e) as being anticipated by Stover et al. (U.S. Patent 5,679,515).

Stover et al. teach a method for identifying agents that modulate an activity of a target cell component wherein a recombinant prokaryotic cell is co-encapsulated in a microenvironment with the agent. The target cell component is a mycobacterial promoter. The recombinant prokaryotic cell is a *Mycobacterium* expressing a luciferase reporter linked to the

promoter. The cell contains a selectable marker, as for example the selectable marker on the plasmid which encodes the promoter and reporter (although it is not clear what is meant by selectable marker in the claim; see the rejection under 35 USC 112 second paragraph, above). The agent is a candidate drug. The goal of the screen is for drugs that inhibit the activity of the promoter, but the screen would also inherently identify agents that increased the promoter activity (although such agents might not be desirable as drugs), and the promoter activity is detected as decreased luminescence resulting from the function of the luciferase enzyme reporter. The microenvironment in which the recombinant mycobacterial cell and agent are co-encapsulated is a cell, such as a macrophage, that is mycobacterium-infectable. The reason Stover et al. are screening for agents in this microenvironment is that mycobacteria naturally infect cells of their hosts. See column 14, lines 20-67, column 15 lines 1-15, and column 22, lines 43-53.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any

evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 54, 55, 58, 59, 62, 63, 67, 68, 69, and 73 rejected under 35 U.S.C. 103(a) as being unpatentable over Stover et al. in view of Valdivia et al. (1996. Gene 173:47-52) and Trias et al. (U.S. Patent 5,989,832).

The teachings of Stover et al. are discussed above. Stover et al. do not teach fluorescent proteins such as green fluorescent protein (GFP).

Valdivia et al. teach applications for green fluorescent protein in the study of host-pathogen interactions. Pathogenic bacteria including *Salmonella, Yersinia*, and *Mycobacteria* that expressed GFP could be detected and sorted in a flow cytometer (FACS) based on the fluorescence of GFP. Valdivia et al. do not teach screening for agents that modulate a target cell component.

Trias et al. teach a method for screening for agents that modulate the activity of non-tetracycline efflux pumps of prokaryotic cells. Agents that inhibit the activity of efflux pumps that export antibiotics out of bacteria are useful for clinical purposes to treat bacteria that are not affected by an antibiotic as a result of the function of the efflux pump. The prokaryotic cells are recombinant since they carry a reporter gene. The expression of the reporter gene is controlled by a regulatory sequence inducible by an adequately high concentration of an antibacterial agent, such that when a bacterium containing the reporter is grown with an agent that inhibits the efflux pump along with an antibacterial agent, such as an antibiotic, the intracellular concentration of

the antibotic will rise, inducing the expresssion of the reporter gene before reaching a growth-inhibitory intracellular concentration. The reporter gene can be, for example, the gene that encodes β-galactosidase, which can be detected by its activity on a detectable substrate. See column 29, lines 7-44 and column 36, Example 2. Among the bacteria encompassed by the invention of Trias et al. are those that can naturally exist within host eucaryotic cells, such as *Salmonella* and *Mycobacteria*. See Trias et al. claims 1, 7, and 11. Trias et al. also teach that the agents can be evaluated "in vivo" for inhibiting the activity of the efflux pumps, and suggest a that for a specific infecting microbe, a cell-based infection model may be used (see column 40, Example 8, and column 41, lines 1-7).

At the time of the invention of the instant application, one of ordinary skill in the art would have been motivated to screen for agents that modulated the activity of a cellular component of a pathogenic microorganism, such as a pathogenic bacterium, because such agents are useful clinically. The cellular component could have been a promoter or another component, such as an efflux pump that exports antibiotics. Recombinant bacterial cells would have had the advantages conferred by easily-screenable reporter genes. For pathogens that naturally invade host cells, such as *Mycobacteria, Salmonella*, and others, it would have been obvious to the ordinary artisan to perform such a screen for agents within the microenvironment of a suitable cell such as a macrophage, because there would have been strong motivation to identify agents that affect bacterial cell component activities in biologically- and clinically-relevant locations. Success would have been expected, based on the teachings of the above references.

Claims 54, 55, 58, 59, 60, 61, 62, 63, 67, 69, 72, 73 are rejected under 35 U.S.C. 103(a) as being unpatentable over Weaver (U.S. Patent 4,643,968, on Applicant's IDS), in view of Weaver (4,916,060, on Applicant's IDS), Trias et al., Rather et al. (U.S. Patent 5,858,367),

Weaver ('968) teach encapsulation of cells in gel microdroplets, and teach that the microdroplets are useful for determining the effects of at least one composition of matter upon a microbiologically active material such as a prokaryotic cell (bacterium) or a eukaryotic cell (yeast or mammalian) cell. Weaver et al. teach that the gel microdroplets are useful to simultaneously determine the count of the cells and their susceptibility to agents. The agents can include small molecules or other cells that secrete a composition that affects the microbiologically active material (cell). The teaching of other cells that secrete a composition would inherently encompass recombinant cells. See abstract, claim 1, and claim 10 of the reference. Weaver et al. also teach the use of dyes (column6). Weaver et al. does not teach a target cell component.

Weaver ('060) teach that fluorescence can be used as an indicator with micro-droplets (see for example claim 1).

Trias et al. teach screening for agents that affect a target cell component that is an efflux pump of a pathogenic bacterial cell. The bacteria taught by Trias et al. include those that naturally can exist within host cells and those that generally do not exist within host cells. Trias et al. do not teach eukaryotic cells as cells affected by an agent, or co-encapsulation of bacterial cells with agents in microenvironments other than a host cell.

Rather et al. teach screening for agents that modulate the activity of a target cell component, wherein the cell is a prokaryote (bacteria) and the component is AarC (see columns

21-22). The cells are recombinant, as they express a *lacZ* reporter which is detectable by color based on a particular substrate (X-Gal). Rather et al. do not teach co-encapsulation.

At the time of the invention of the instant application, one of ordinary skill in the art would have been motivated to screen for agents that modulated the activity of a cellular component, either to gain information about the activity of the component or to identify drugs, such as antibiotics. The cellular component could have been a promoter or another component, such as an efflux pump that exports antibiotics. It would have been useful, as taught by Weaver ('968) to use gel microdroplets, since these allow for enumeration of cells and detection of particular activities. For example, in the method of Trias et al. with respect to bacteria that do not normally exist within host cells, it would have been desirable to assay for both the effect of an agent on the efflux pump, based on the reporter screen, and to enumerate the bacteria, to determine whether the agent, after affecting the reporter, did promote killing of the bacteria by the antibiotic. Thus, the microdroplets of Weaver would have provided useful modifications to any teachings of screens for agents that modulate an activity of a target cell component, such as that of Trias et al., or Rather et al., for example. Success in detection with fluorescent or visible dyes would have been expected, based on the teachings of Weaver (both references). Success would have been expected, based on the teachings of the above references.

Allowable Subject Matter

Claims 56, 57, 64-66, and 70-71 objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims and including addressing the rejection under 35 USC 112 second paragraph of claim 70.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lisa J. Gansheroff whose telephone number is (703) 605-1203. The examiner can normally be reached 9 AM - 5 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader can be reached at (703) 308-0447. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242 for regular communications. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the patent analyst Dianiece Jacobs whose telephone number is (703) 305-3388 or to the receptionist whose telephone number is (703) 308-0196.

LG
April 1, 2001

JAMES KETTER
PRIMARY EXAMINER